

A Phase I Trial and Pharmacokinetic Study of 9-*cis*-Retinoic Acid (ALRT1057) in Pediatric Patients with Refractory Cancer: A Joint Pediatric Oncology Branch, National Cancer Institute, and Children's Cancer Group Study¹

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ABSTRACT

Purpose: To determine the maximum tolerated dose and describe the toxicities of 9-*cis*-retinoic acid (9cRA, ALRT1057) administered p.o. tid in pediatric patients with refractory cancer and to study the pharmacokinetics of 9cRA and determine whether systemic drug exposure changes with chronic dosing.

Patients and Methods: Children with refractory cancer (stratified by age, ≤ 12 and > 12 years) were treated with p.o. 9cRA for 28 consecutive days. The starting dose was 50 mg/m²/day divided into 3 doses with planned escalations to

65, 85, and 110 mg/m²/day. Pharmacokinetic sampling was performed on days 1 and 29 of the first cycle.

Results: Of the 37 patients entered, 18 patients ≤ 12 years of age and 11 patients > 12 years of age were evaluable for toxicity. In patients > 12 years of age, dose-limiting headache occurred in 2/2 patients at the 110 mg/m²/day dose level; 1/8 patients at 85 mg/m²/day developed dose-limiting pseudotumor cerebri. In patients ≤ 12 years of age, 3/5 patients at the starting dose level of 50 mg/m²/day developed dose-limiting pseudotumor cerebri; and 0/6 patients experienced dose-limiting toxicity at 35 mg/m²/day. Reversible non-dose-limiting hepatotoxicity was observed in 15 patients across all of the dose levels. There was considerable interpatient variability in 9cRA plasma concentrations. Peak plasma concentrations of 9cRA occurred at a median of 1.5 h after a p.o. dose, and the harmonic-mean terminal half-life was 43 min. By day 29 of 9cRA administration, the plasma 9cRA area under the curve declined by an average of 65% from day 1 values.

Conclusions: The dose-limiting toxicity of 9cRA in pediatric patients was neurotoxicity, primarily pseudotumor cerebri. Younger children tolerate significantly lower doses of 9cRA than older children. Similar to all-*trans*-retinoic acid, the pharmacokinetics of 9cRA demonstrated a wide degree of interpatient variability and decreased over time when administered on a daily basis. The recommended Phase II dose of 9cRA in patients ≤ 12 and > 12 years of age is 35 and 85 mg/m²/day, respectively.

INTRODUCTION

Retinoids (naturally occurring and synthetic analogues of vitamin A or retinol) play a pivotal role in the regulation of growth and development, vision, reproduction, cell differentiation, and immune function (1). In preclinical studies, retinoids induce differentiation and/or arrest tumor cell growth in a variety of pediatric cancers, including neuroblastoma (2, 3), Wilms' tumor (4), osteosarcoma (5–8), and rhabdomyosarcoma (9–12). As a therapeutic agent, the naturally occurring retinoid ATRA³ successfully induces complete remissions in a high proportion of patients with acute promyelocytic leukemia; as chemopreventive agents, topical and p.o. retinoids are effective for the treatment of premalignant skin conditions and cervical dysplasia

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³ The abbreviations used are: ATRA, all-*trans*-retinoic acid; 9cRA, 9-*cis*-retinoic acid; 13cRA, 13-*cis*-retinoic acid; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; AUC, area under the curve; CRABP, cellular retinoic acid binding protein.

and for the prevention of second primary tumors in patients with head and neck cancer (13).

Retinoids exert their diverse biological effects through interaction with specific nuclear receptors. The two families of retinoid nuclear receptors that have been described, the RARs (14, 15) and the RXRs (16, 17), have ligand-binding domains, which share only 29% homology. The RARs bind the naturally occurring retinoid ATRA with high affinity, whereas the RXRs are activated by but do not bind to ATRA, indicating that an active metabolite of ATRA is responsible for its RXR-related transcriptional activity (18). 9cRA, a geometric isomer of ATRA, is a naturally occurring biologically active retinoid (19), which is capable of binding and transactivating both the RXRs and the RARs (14–16). This may, in part, account for its enhanced potency compared with ATRA in inhibiting the growth and inducing the differentiation of a spectrum of human tumors *in vitro* (20–23). Another difference between 9cRA and ATRA relates to the binding of these isomers to the CRABPs. CRABPs are cytoplasmic proteins believed to regulate the amount of retinoid reaching and binding nuclear receptors (24, 25). Up-regulation of CRABPs could therefore diminish the potential effectiveness of retinoids. In contrast to ATRA, CRABPs do not bind 9cRA (26); therefore, 9cRA would not be susceptible to this potential mechanism of retinoid resistance.

Of the pediatric solid tumors, the action of retinoids in neuroblastoma has been the most extensively studied. Although 13cRA, a retinoic acid isomer that binds neither class of receptors and likely acts as a prodrug for ATRA, did not demonstrate significant activity in children with refractory neuroblastoma (27), it did improve survival in patients with high-risk neuroblastoma when administered at a time of minimal residual disease (28). Clinical activity in refractory neuroblastoma was observed in a pediatric Phase I trial of ATRA with interferon- α 2a (29) and is being studied in a Phase II trial. In comparing the activity of the retinoic acid isomers in preclinical models of neuroblastoma, several studies have suggested that 9cRA may be the more potent isomer (22, 30–37). On the basis of this preclinical and clinical data, we performed a Phase I trial of 9cRA in pediatric patients with refractory malignancies.

Adult trials defined the MTD of 9cRA to be between 100 and 140 mg/m²/day (38–40). In adult patients, headache was the most common toxicity observed and was dose limiting. Other toxicities commonly observed included cheilitis, dry skin, conjunctivitis, diarrhea, hypertriglyceridemia, and hypercalcemia. Because our previous experience with ATRA suggested that children were more sensitive than adults to the neurotoxic effects of retinoids, the starting dose for this pediatric Phase I trial was 50 mg/m²/day, representing 50% of the adult MTD.

MATERIALS AND METHODS

Patient Eligibility. Patients \leq 21 years of age with histologically confirmed cancer refractory to conventional therapy were eligible for this trial. Patients must have recovered from the toxic effects of previous therapy and had to be able to swallow capsules. All of the patients had adequate hepatic and renal function as defined by a serum bilirubin $<$ 1.5 mg/dl, serum transaminases less than twice the upper limit of normal,

Table 1 Characteristics of the 29 patients who were evaluable for toxicity

Age cohort	\leq 12 years	$>$ 12 years
Median age in yrs (range)	7 (2–11)	17 (14–21)
Sex (M/F)	7/4	15/3
Median no. of previous regimens (range)	3 (1–5)	2 (1–6)
Diagnoses		
Osteosarcoma	5	0
Neuroblastoma	3	4
Ewing's sarcoma	3	2
Rhabdomyosarcoma	3	0
Desmoplastic small cell tumor	1	0
Synovial cell sarcoma	1	0
Mesenchymal chondrosarcoma	1	0
Adenosquamous carcinoma	1	0
ALL	0	2
Teratocarcinoma	0	1
Hepatoblastoma	0	1
Wilms' tumor	0	1

and a serum creatinine $<$ 1.5 times normal for age. Patients evaluable for hematological toxicity were required to have a granulocyte count \geq 1,500/mm³ and a platelet count \geq 100,000/mm³. Patients with tumor infiltrating bone marrow or with a history of previous extensive radiation were considered inevaluable for hematological toxicity. Patients with primary or metastatic central nervous system tumors, seizure disorder, hydrocephalus, or pseudotumor cerebri were excluded from the study. Before study entry, informed consent was obtained from the patient or his/her guardian in accordance with individual institutional policies.

Trial Design. 9cRA (ALRT1057) was manufactured by Ligand Pharmaceuticals as 10-mg and 25-mg oval soft gelatin capsules and supplied by the Cancer Therapy Evaluation Program of the National Cancer Institute.

The starting dose of 9cRA was 50 mg/m²/day divided into three doses, with planned dose escalations to 65, 85, and 110 mg/m²/day. The results of our previous pediatric Phase I trial (41) suggested that younger patients may be more susceptible to the neurological toxicity of retinoids than older children and adults. Therefore, patient entry on this trial was stratified by age into two groups, \leq 12 years and $>$ 12 years of age, and the dose escalated separately in these two groups.

The MTD of 9cRA was defined as the highest dose level at which less than two of a cohort of three to six patients experienced a DLT. At least three patients within a cohort had to be evaluable for toxicity before escalating to the next higher dose level. If one of the first three patients entered at a dose level experienced DLT, an additional three patients were entered at that dose level. Inpatient dose escalation was not allowed. Toxicities were graded according to the NCI Common Toxicity Criteria, version 1 (42). Hematological DLT was defined as grade 4 neutropenia or thrombocytopenia of $>$ 5 days duration. Nonhematological DLT was defined as any grade 3 or 4 nonhematological toxicity with the specific exclusion of grade 3 nausea and vomiting or grade 3 fever.

Patients who experienced a DLT while receiving 9cRA had the drug withheld for one week of the cycle. After one week, if

Table 2 Dose-limiting neurotoxicity of 9cRA in children stratified by age into >12 yrs and ≤12 yrs of age

Age	Dose level (mg/m ² /day)	No. of patients			DLT observed
		Entered	Evaluable	DLT	
>12 yr old cohort	50	6	5	0	
	65	3	3	0	
	85 ^a	12	8	1	Pseudotumor cerebri
	110	2	2	2	Grade 4 headache
≤12 yr old cohort	35 ^a	8	6	0	
	50	6	5	3	Pseudotumor cerebri

^a Maximum tolerated dose of 9cRA.

Table 3 Non-dose limiting toxicities (grade ≤2) observed during the first cycle of 9cRA^a

	≤12 years	>12 years
Headache	6	19
Hypertriglyceridemia	5	14
Hepatic	5	10
Nausea	2	11
Dry lips	3	8
Dry skin	4	7
Abdominal discomfort		3
Dry eyes		2
Hypercalcemia	1	1
Arthralgias		1
Bone pain		1
Hirsutism	1	
Joint effusion		1
Tinnitus		1

^a No. of patients are shown for each type of toxicity.

the DLT was reversible as documented by return to Grade ≤2 toxicity, patients could resume 9cRA at the next lower dose level.

Pharmacokinetics. Pharmacokinetic studies were performed on days 1 and 29 of the first cycle. On the days of pharmacokinetic monitoring, after an overnight fast, the 9cRA dose was administered with 4–8 ounces of whole milk. Heparinized blood samples were obtained immediately before the dose, and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, and 8.0 h after the dose. Plasma was separated from blood cells by centrifugation, protected from light, and stored at –70°C until assayed.

The plasma concentration of 9cRA was measured by a modification of a high-performance liquid chromatography method described previously (43, 44). The AUC from 0 to 8 h was calculated by the trapezoidal method (45). Samples below the limit of detection (0.03 μM) obtained immediately before the first detectable time point or immediately after the last detectable time point were set to 0.03 μM. All of the other samples below the limit of detection were set equal to 0. Extrapolation of the AUC after the last time point was not performed because of the limited number of data points available to accurately estimate the terminal elimination in the majority of patients. In patients with a minimum of three data points on the terminal portion of the plasma-concentration time curve, the terminal half-life was estimated by regression analysis.

Table 4 Maximum grade of hepatotoxicity observed with 9cRA^a

Dose level (mg/m ² /day)	No. evaluable patients	Grade of hepatotoxicity			
		1	2	3	4
35	6	1	2		
50	10		1 ^b		
65	3	3			
85	8	5	1		
110	2				

^a Number of patients are shown for each grade.

^b Patient treated at 50 mg/m²/day who developed grade 2 hepatotoxicity was >12 years of age.

RESULTS

Toxicity. Twenty three patients (18 evaluable for toxicity) ≤12 years of age and 14 patients (11 evaluable for toxicity) >12 years of age were entered onto the trial. Reasons that patients were not evaluable for toxicity included progressive disease before completing cycle 1 (n = 4), incorrect dose (n = 1), noncompliance (n = 1), patient withdrawal (n = 1), and intratumoral hemorrhage requiring surgery (n = 1). The patient who developed intratumoral hemorrhage on day 20 of his initial cycle had a platelet count of 229,000/mm³ and a prothrombin time/partial thromboplastin time of 10.6/24.7 s at the time of the bleeding episode. Therefore, the hemorrhage was attributed to progressive disease. The toxicity profile in the other inevaluable patients did not differ from the remainder of the patient population. The characteristics of the patient population are shown in Table 1. Eleven patients >12 years and 4 patients ≤12 years of age were evaluable for hematological toxicity. Twenty-two patients received 1 cycle, 4 patients received 2 cycles, 1 patient received 3 cycles, and 2 patients received 4 cycles of therapy.

In patients ≤12 years of age, three of five evaluable patients who were treated at the starting dose level of 50 mg/m²/day developed dose-limiting pseudotumor cerebri. Two of the three patients developed non-dose-limiting headaches within the first week of dosing. Pseudotumor cerebri was diagnosed on days 17 and 26 of the first cycle in these patients. The third patient tolerated the initial cycle of 9cRA but was found to have asymptomatic papilledema on day 8 of the second cycle. Therefore, subsequent patients in this age strata were treated at a lower dose level of 35 mg/m²/day. None of the six evaluable patients ≤12 years experienced DLT at this dose level. The MTD in patients ≤12 years of age is 35 mg/m²/day (Table 2).

In the >12 years of age stratum, dose-limiting headache

Table 5 Pharmacokinetic parameters obtained on the first day of 9cRA administration

Dose level		Cmax μM (mean \pm SD)	AUC $\mu\text{M}\cdot\text{min}$ (mean \pm SD)	Half-life min harmonic-mean (range)
(mg/m ² /d)	No. patients			
35	7	0.33 \pm 0.09	40 \pm 18	32 (26–41)
50	11	0.76 \pm 0.55	109 \pm 98	38 (15–41)
65	3	0.23 \pm 0.1	35 \pm 19	64 (41–97)
85	9	0.97 \pm 0.56	132 \pm 132	51 (23–140)
110	2	0.89 \pm 0.3	154 \pm 54	70 (60–84)

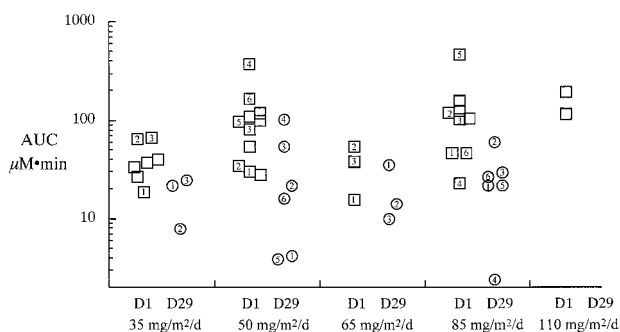


Fig. 1 Plasma AUC_{0–8h} on day 1 (□) and day 29 (○). Wide interpatient variability is observed at all dose levels. Numbers indicate paired patient specimens within dose levels. AUC decreased by a median of 74% (range 5–96%) by day 29 of treatment.

occurred on days 1 and 5 of the initial cycle of 9cRA treatment in the two patients who were treated at the 110 mg/m²/day dose level. One of eight evaluable patients who were treated at the 85 mg/m²/day dose level developed pseudotumor cerebri, which was detected during the third cycle of 9cRA (Table 2). These central nervous system symptoms resolved within 1 week of discontinuation of drug, and 3/3 patients who continued on treatment tolerated a reduced dose of 9cRA. The MTD in patients >12 years of age is 85 mg/m²/day.

Headache and elevations in serum triglycerides and hepatic transaminases were the most frequent non-dose-limiting toxicities observed (Table 3). Nausea was observed but was not usually associated with vomiting. Dry skin and dry lips also occurred relatively frequently but usually were readily managed with topical emollients. The hepatotoxicity observed in 13 patients was reversible and non-dose-limiting (Table 4). The median (range) peak alanine aminotransferase and aspartate aminotransferase in these patients was 86 units/liter (22–296 units/liter) and 87 units/liter (38–219 units/liter), respectively.

Responses. No complete or partial responses were observed.

Pharmacokinetics. Thirty-two patients had pharmacokinetic sampling performed with the first dose of 9cRA, and 19 patients also had pharmacokinetic sampling after 28 consecutive days of drug administration. There was considerable interpatient variability in 9cRA concentrations observed across all of the dose levels, but there was a trend toward a proportional increase in maximum concentration and AUC with increasing dose. The pharmacokinetic parameters are summarized in Table 5. There was no relationship between apparent clearance and patient age

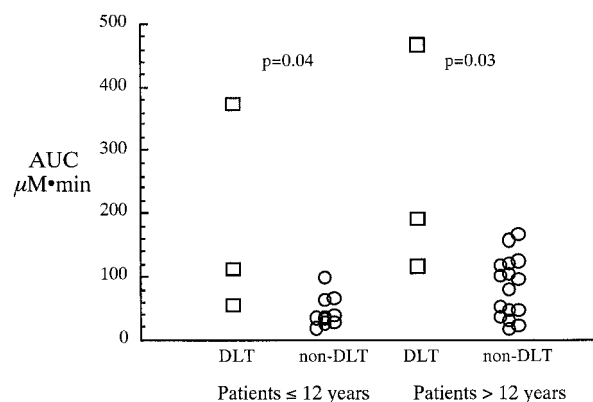


Fig. 2 Patients with dose-limiting neurotoxicity (□) had a significantly higher day 1 AUC than patients without DLT (○; Mann-Whitney *U* test).

(data not shown). The median time to peak concentration occurred 1.5 h after a p.o. dose, with a range of 0.5–3 h. The harmonic-mean terminal half-life of 9cRA was 43 min, with a range of 15–140 min.

By day 29 of 9cRA administration, the plasma 9cRA AUC declined by a median of 74% (range 5–96%) from the day 1 values (Fig. 1). All of the 19 patients studied on days 1 and 29 experienced a decrease in plasma 9cRA exposure over the 28 days of treatment.

Pharmacodynamics. The plasma 9cRA AUC (Fig. 2) in patients who experienced dose-limiting neurotoxicity (median AUC 154 $\mu\text{M}\cdot\text{min}$; range 54–467 $\mu\text{M}\cdot\text{min}$) was significantly greater ($P = 0.005$; Mann-Whitney *U* test) than that observed in patients who did not experience DLT (median AUC 50 $\mu\text{M}\cdot\text{min}$; range 16–167 $\mu\text{M}\cdot\text{min}$). However, the considerable overlap in AUC between the groups suggests that pharmacokinetic monitoring to prevent neurotoxicity may not be feasible. A trend was also found for higher peak 9cRA plasma concentrations in patients with dose-limiting neurotoxicity (data not shown).

DISCUSSION

Of the retinoic acid isomers in clinical use, 9cRA is considered a pan-agonist because of its ability to bind to both the RAR and RXR receptors. In this pediatric Phase 1 trial, we found that the toxicity spectrum and pharmacokinetic behavior of 9cRA was similar to that of ATRA. Neurotoxicity was the DLT in children, and similar to our previous experience with ATRA (29, 41), younger children were more susceptible than

older children. In general, children were less tolerant of the neurotoxic effects than adults. The MTD observed in two adult Phase I trials ranged between 100 and 140 mg/m²/day (38, 39) with headache being the DLT. In this pediatric trial, the MTD in children ≤12 years and >12 years of age was 35 and 85 mg/m²/day, respectively. A pharmacokinetic basis for the differences in tolerability between younger children, older children, and adults was not found.

Minor reversible elevations in hepatic transaminases were frequently noted at all of the dose levels and did not appear to be dose related (Table 4). The other most commonly observed non-dose-limiting toxicities observed in this trial were similar to those observed with ATRA and included hypertriglyceridemia, nausea, dry skin, and cheilitis. This side effect profile is also similar to that observed in adult patients treated with 9cRA. Because only seven patients received the drug for more than one cycle, long-term tolerability of 9cRA cannot be readily assessed.

The pharmacokinetics of 9cRA were similar to those observed with ATRA and stand in contrast to those observed with 13cRA. A wide degree of interpatient variability was observed at all of the dose levels. After 28 days of consecutive daily administration, plasma drug concentrations decreased by an average of 65% relative to that observed on day 1 of drug administration. The magnitude of this decrease, presumably attributable to an autoinduction of metabolism, appears to be less than that observed with ATRA, but given the wide interpatient variability, a definitive conclusion cannot be made. Despite their structural similarity, pharmacokinetic studies of 13cRA, ATRA, and 9cRA demonstrate substantial differences in drug disposition. 13cRA has a prolonged elimination phase with a terminal half-life of 12–24 h (46, 47), whereas 9cRA and ATRA are eliminated considerably more rapidly with a half-life of ~45 min (41, 48, 49). In addition, with chronic administration, plasma concentrations of ATRA and 9cRA decline significantly over time, a phenomenon not observed with chronic 13cRA dosing (50). These differences may relate to the fact that, whereas 9cRA and ATRA bind nuclear receptors, 13cRA does not and presumably functions as a prodrug for these active isomers.

Currently all three of the retinoic acid isomers are available for clinical study. Although preclinical studies suggest that 9cRA may be the more potent of the isomers in terms of inducing differentiation, it is not clear that this will translate into a clinically observable advantage over ATRA or 13cRA. The Children's Cancer Group trial of 13cRA in the setting of minimum residual disease in children with neuroblastoma support the laboratory observations made over the past 20 years that retinoids may prove useful in the treatment of neuroblastoma. Determining the optimal retinoic acid isomer to use and defining the how best to integrate retinoids with cytotoxic agents remain future challenges.

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